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Surgical and Clinical Risk Factors of Postoperative Hypocalcemia after Total Thyroidectomy

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Abstract

Introduction: Hypocalcemia is the most common complication of total thyroidectomy. It is important to identify and avoid high-risk surgical techniques to lower the rate of this complication. Additionally, by knowing risk factors of hypocalcemia, lower risk patients can be discharged earlier. In this study we aim to understand the surgical, patient-related, and disease-related and laboratory risk factors of transient hypocalcemia after total thyroidectomy.

Methods: Patients undergoing total thyroidectomy were prospectively recruited. Various variables including status of parathyroid glands and the location of thyroid arteries ligation were recorder during the surgery. Serum PTH levels were measured at the baseline and one hour, 24 hours and one month after the surgery. Statistical analysis was performed to assess the association of study variables with the rate of hypocalcemia.

Results: The rate of hypocalcemia was significantly higher in the more advanced tumors. Number of identified parathyroid glands resulted in lower risk of hypocalcemia. Change in PTH levels from the baseline, both one hour and 24 hours after the surgery, and not the absolute PTH levels was significantly associated with hypocalcemia.

Age, sex, tumor size, pathology of the tumor, extent of the surgery, ischemic discoloration or autotransplantation of parathyroid glands and distal location of thyroid arteries ligation was not significantly associated with hypocalcemia.

Conclusion: Proper surgical techniques and identification of the parathyroid glands is important in preventing hypocalcemia after total thyroidectomy. Additionally, for predicting hypocalcemia the relative and not absolute PTH levels should be more emphasized.

Keywords: Total thyroidectomy; Hypocalcemia; Surgical techniques; Parathyroid hormone

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Introduction

Total Thyroidectomy (TT) is one of the most common endocrine surgeries [1]. It is the treatment of choice for the patients with malignant thyroid tumors as well as patients with multinodular goiters who experience compression symptoms. The most common complication of total thyroidectomy is post-operative hypocalcemia due to hypoparathyroidism [2]. This complication is relatively common with an incidence of 20% to 30%, perhaps due to the sensitivity of parathyroid glands and their supplying arteries to trauma during surgery [3]. However, most cases of post-TT hypocalcemia are transient, and the rate of permanent hypocalcemia persisting 12 months after the surgery is less than 2% [4]. Post-TT hypocalcemia is associated with significant morbidity and healthcare costs, but is rarely fatal [1]. Therefore, it is important to identify and avoid high-risk surgical techniques and management practices that are associated with higher incidence of hypocalcemia.

Post-TT hypocalcemia usually does not become evident in the first 24 hours to 48 hours. Therefore, patients are routinely hospitalized for two days after the surgery to monitor for the clinical and laboratory signs of hypocalcemia [5]. However, this approach causes significant costs for the healthcare system and the patient and patients who are at a lower risk of developing hypocalcemia, do not benefit from a lengthy hospitalization. There is currently a trend toward discharging lower risk patients at the same day of the surgery, or even performing total thyroidectomy as an outpatient procedure [6]. However, it is not safe to use this approach for all the patients, since patients developing hypocalcemia after being discharged experience significant distress and need to visit the emergency department [7]. Therefore, it is important to identify risk factors that can predict the risk of developing hypocalcemia. The aim of this study was to identify surgery-related, disease-related, patient-related and laboratory risk factors that are associated with transient hypocalcemia after total thyroidectomy.

Materials and Methods

From January 2016 to September 2018, forty-four patients who underwent total thyroidectomy at the Ears, Nose and Throat Department of Ghaem Hospital and Omid Hospital at Mashhad, Iran were prospectively recruited in this study. The included patients were not limited to any specific type of tumor. Patients with subtotal thyroidectomy, laryngectomy or with a history of previous lobectomy were excluded. The study was approved by the Ethics Committee of the Mashhad University of Medical Sciences and an informed consent was received from all the patients.

The same surgical team performed all the surgeries. Neck dissection was performed if an involved lymph node was suspected in physical examination, in ultrasound or during the surgery. In these cases, the harvested lymph nodes were examined by a pathologist and the number of metastatic lymph nodes was recorded. In cases that parathyroid glands were accidentally removed, they were autotransplanted on the Sternocleidomastoid (SCM) muscle. During the surgery, the number of identified, excised, ischemic and autotransplanted parathyroid glands, the location of thyroid arteries ligation (distal or proximal), the recurrent laryngeal nerves status, the size of the thyroid gland, the size of the tumor and the position of the tumor inside the thyroid (left or right) was recorded.

Serum PTH levels were measured at the baseline and one hour, 24 hours and one month after the surgery. Cobas E411 auto-analyzer (Roche Diagnostics, Switzerland) was used for the measurement of serum PTH levels with a normal range of 10 pg/mL to 65 pg/mL. Serum Ca levels were measured three times daily after the surgery until discharge and then one month later. Patients were discharged after two days if the calcium levels were consistently within the normal range of 8.4 mg/dL to 10.2 mg/dL. Ca supplements in oral or intravenous forms were administered if the level of calcium was below 7 mg/dL or was consistently decreasing, or if the patient developed signs or symptoms of hypocalcemia including paresthesia of extremities, Chvostek's sign and Trousseau's sign. Additionally, a group of patients received Ca supplement before developing clinical or laboratory hypocalcemia at the surgeon's discretion.

Statistical analysis was performed using IBM SPSS 25 (IBM Corp., Armonk, NY, USA). Categorical variables were reported as frequencies and continuous variables as mean +/- standard deviation. The association of hypocalcemia with categorical variables was evaluated using Chi-Squared test or Fischer's exact test. Lilliefors (Kolmogorov-Smirnov) and Shapiro-Wilk's tests were used to assess the normality of continuous variables. The normally distributed variables were compared between the groups using ANOVA with Duncan's post-hoc test. Non-normal variables were compared using Kruskal-Wallis test, and post-hoc pairwise Mann-Whitney was performed for the statistically significant variables to determine the groups that are different from each other. The level of significance was set at $p<0.05$ for all tests.

Results

Forty-four patients including 30 females (68.2%) and 14 males (31.8%) participated in this study. The mean age of the participants was 43.9 years ± 11.7 years. Seventeen patients (38.6%) developed hypocalcemia and received calcium supplements therapy. The pathology of the tumor was Papillary Thyroid Carcinoma (PTC) in 33 (75.0%), Follicular Thyroid Carcinoma (FTC) in 3 (6.8%), Modularly Thyroid Carcinoma (MTC) in 1 (2.3%) and benign in 7 patients (15.9%). The mean size of the tumors was 3.59 cm ± 4.75 cm. Among the malignant tumors, 25.0% were at stage I, 17.9% at stage II, 50.0% at stage III and 7.1% at stage IV. The stage of the tumor was significantly associated with hypocalcemia ($p < 0.05$), with stage III having the highest prevalence of hypocalcemia. However, pathology ($p=0.344$) and size of the tumor ($p=0.304$) were not significantly predictive of hypocalcemia.

Neck dissection was performed in 22 patients (50.0%), including combined central and lateral neck dissection in 11 (25.0%), isolated Central Neck Dissection (CND) in 7 (15.9%) and isolated Lateral Neck Dissection (LND) in 4 patients (9.1%). The mean number of total, central and lateral metastatic lymph nodes was 4.35 ± 4.52, 1.60 ± 2.13 and 3.90 ± 3.70, respectively. Hypocalcemia was not associated with performing neck dissection ($p=0.476$) and the number of metastatic lymph nodes ($p=0.247$).

All four parathyroid glands were identified in 10 patients (22.7%) and none were identified in 14 patients (31.8%). The number of observed parathyroid glands was significantly associated with hypocalcemia ($p<0.05$). In seven cases (15.9%) at least one parathyroid gland was excised, and in two cases (4.5%) one parathyroid gland was autotransplanted in the SCM muscle. The rate of hypocalcemia was not significantly associated with the number of excised parathyroid glands ($p=0.907$) and performing parathyroid gland autotransplantation ($p=0.712$). At least one parathyroid gland developed ischemic discoloration in seven cases (15.9%). The number of ischemic parathyroid glands was not associated with hypocalcemia ($p=0.296$). All inferior and superior thyroid arteries were ligated distally in 88.6% of the cases. In one case the left recurrent laryngeal nerve was not seen and in another case both recurrent laryngeal nerves were not seen. For both these cases tracheostomy was performed.

Thirteen patients (76.4%) with hypocalcemia, developed signs or symptoms of hypocalcemia within the first 48 hours and two patients (11.7%) after the first 48 hours. Two patients (11.7%) did not develop signs or symptoms of hypocalcemia. Four patients (23.5%) had both signs and symptoms of hypocalcemia, whereas nine patients (53.0%) complained of paresthesia with no signs of hypocalcemia, and two patients (11.8%) had only signs of hypocalcemia. Of the 27 patients who did not develop hypocalcemia, 11 patients (40.7%) received calcium on the first day after surgery at the surgeon's discretion.

The mean PTH levels dropped from a baseline level of 57.47 pg/mL ± 26.99 pg/mL to 18.43 pg/mL ± 16.40 pg/mL at the first hour and 15.42 pg/mL ± 11.94 pg/mL at the first day after the surgery, and gradually increased to 28.97 pg/mL ± 17.73 pg/mL one month after the surgery. Absolute PTH levels before, 1 hour; 24 hours and one month after the surgery were not significantly associated with hypocalcemia. However, the change in PTH values one and 24 hours after the surgery compared to baseline was significantly associated with hypocalcemia ($p<0.05$). On average, PTH levels in hypocalcemia group decreased 76.5% ± 16.5% at the first hour and 79.9% ± 14.8% at the first day after the surgery.

In the hypocalcemia group, the mean level of calcium was significantly lower than the other two groups from the first measurement until the day of discharge ($p<0.05$) but reached the same level ($p=0.779$) after a month.

Discussions

Various surgical, disease-related, and patient-related and biochemical factors can influence the risk of post-TT hypocalcemia. Surgeons can identify low-risk patients by knowing these risk factors and avoid unnecessary hospitalizations and its associated healthcare costs. Additionally, by identifying surgical practices resulting in higher risk of hypocalcemia, they can attempt to avoid these high-risk techniques.

It has been shown that total thyroidectomy performed by less experienced surgeons is associated with higher rates of complications [8]. Trauma, incidental excision and damage to the blood supply of parathyroid glands during surgery can transiently or permanently impair parathyroid glands function. In this study we investigated several surgery-related variables as risk factors for post-TT hypocalcemia.

The recommended surgical strategy to prevent post-TT hypocalcemia is to carefully identify and preserve the parathyroid glands and their blood supply. We found that the greater number of parathyroid glands identified during the surgery is associated with the lower risk of hypocalcemia. It has been shown that identification of less than two parathyroid glands results in a four-fold increase in the risk of permanent but not transient hypocalcemia [9]. However, some studies have argued that identifying the lower number of parathyroid glands decreases the risk of post-TT hypocalcemia, perhaps since attempts to visualize parathyroid glands can damage the glands and their blood supplies [10,11].

The mere identification of parathyroid glands does not necessarily lead to the preservation of the gland and its blood supplies [10]. Occasionally the blood supply to the glands is damaged and results in ischemic discoloration. We observed ischemic discoloration of at least one parathyroid gland in seven cases and we found that it did not increase the risk of developing hypocalcemia. Additionally, in seven cases, at least one of the parathyroid glands was excised and in two cases one parathyroid gland was autotransplanted on the SCM muscle. In line with the findings of a number of previous studies, we found no association between the numbers of excised parathyroid glands with the rate of hypocalcemia [12-14]. However, it was shown by a meta-analysis that incidental excision of parathyroid glands causes a two-fold higher risk of transient hypocalcemia [15]. Furthermore, we found no association between autotransplantation and the risk of hypocalcemia. The same meta-analysis showed that the risk of transient hypocalcemia is increased by an odds ratio of 2.03 in patients who had parathyroid gland autotransplantation [15]. The lack of this finding in our study could be due to the very few incidents of parathyroid glands autotransplantation.

Several authors have argued that the distal ligation of the thyroid arteries closer to the thyroid capsule preserves the parathyroidal branches better and theoretically leads to lower rates of hypocalcemia [11,16]. In our study we ligated 94.8% of the thyroid arteries distally and found no association between the sites of the thyroid arteries ligation with the risk of transient hypocalcemia. Recently, a randomized controlled trial and a meta-analysis have concluded the same [17,18]. In contrast, another meta-analysis showed that the proximal ligation of inferior thyroid artery increases the risk of transitional and not permanent hypocalcemia [19].

Central and/or lateral neck dissection was performed in 50.0% of the participants and was not associated with a higher risk of hypocalcemia. Similarly, Noureldine et al., [20] compared the rate of hypocalcemia in patients undergoing thyroidectomy with and without central neck dissection and found no difference. However, a randomized controlled trial showed that patients who undergone prophylactic central neck dissection were at a higher risk of developing transient and permanent hypocalcemia [21]. Moreover, it has been shown that performing central neck dissection is associated with higher rates of incidental excision of parathyroid glands [22]. Additionally, similar to a study by Turanli et al., [23] we found no significant association between hypocalcemia and the number of metastatic lymph nodes.

In our study, the higher stage of the thyroid carcinomas was associated with a higher risk of hypocalcemia, which perhaps was due to the more extensive surgery required for these cases. Similarly, Burge et al., [24] showed that each increase in the stage of thyroid cancer could double the odds of developing permanent hypocalcemia. We also investigated the association of the pathology or FNA results of the tumor with hypocalcemia and found no association. A meta-analysis found that patients with Graves's disease were at a higher risk of developing transient hypocalcemia, but we did not observe such association in our study [15].

Previous studies have reported conflicting results regarding the association of age with the risk of hypocalcemia, but a meta-analysis showed that there is no significant difference in the mean age between patients with and without transient hypocalcemia [15]. We similarly found no association between age and hypocalcemia. We also observed no difference in the rate of hypocalcemia in men and women. On the contrary, the same meta-analysis and several other studies showed that the female patients are at a two-fold higher risk of developing transient hypocalcemia compared to men [15,25-27].

The accuracy of serum PTH level in predicting post-TT hypocalcemia has been a subject of debate in the literature for a long time. Recently, a systematic review including 69 studies reported that 62 studies concluded that PTH level can predict hypocalcemia. However, the authors argued that there was a significant heterogeneity between studies regarding the timing of PTH measurement, PTH thresholds and definitions of hypocalcemia. They showed that across the included studies the median accuracy of the absolute PTH level and its change from baseline was 86% and 89%, respectively [28]. Moreover, a meta-analysis on fourteen studies showed that both intra- and post-operative PTH levels were significantly lower in patients who developed hypocalcemia [29]. In our study however, we observed no relationship between the absolute PTH levels and the rate of hypocalcemia. Rather, we identified that the change in PTH levels from the baseline, both one hour and 24 hours after the surgery, was significantly associated with hypocalcemia. In a meta-analysis, Noordzij et al., [3] analyzed percent change rather than the absolute values of PTH and showed that a decrease in PTH levels greater than 70% one hour after the surgery is predictive of hypocalcemia with a sensitivity of 93.3% and specificity of 88.0%. Additionally, Mathur et al., [28] in their systematic review reported that a decrease in PTH levels greater than 70% can predict hypocalcemia with a median sensitivity and specificity of 93.1% and 90.0%, whereas absolute PTH levels below 15 pg/mL predicts hypocalcemia with a median sensitivity and specificity of 83.4% and 87.0%. Although a larger multi-center or a meta-analytic study is needed to specifically compare the predictive accuracy of absolute versus relative values of PTH, based on the current evidence we recommend utilizing percent change rather than absolute values of PTH to identify higher risk patients.

We observed that on average, the PTH levels in the hypocalcemia group decreased 76.5% at the first hour and 79.9% at the first day after the surgery to levels below the normal range. The post-operative PTH levels in patients without hypocalcemia decreased as well, but stayed within the normal range. After a month, although the average PTH level for all the patients with and without hypocalcemia was within the normal range it failed to return to the baseline level. However, at the same time the majority of the patients were normocalcemic, while receiving calcium supplements. A similar study following the course of PTH level over time in patients with post-TT hypoparathyroidism showed that 73% of the patients after a week and 82% of the patients in the long-term follow-up fully recovered to a PTH level above 10 pg/mL [30].

In our study, 38.6% of the patients developed hypocalcemia. The majority of these patients developed clinical manifestations of hypocalcemia while only two patients were asymptomatic. However, in previous studies the majority of the patients with hypocalcemia develop no signs or symptoms [16,31]. Moreover, on the contrary to the usual delayed presentation of hypocalcemia after total thyroidectomy, in this study the majority of the patients showed the clinical manifestations of hypocalcemia within the first 48 hours.

Limitations

The power of our study was limited by the small number of participants. We had very few incidents of parathyroid glands excision, ischemic discoloration and autotransplantation, and our results regarding the effect of these variables on the rate of hypocalcemia is not highly reliable. We failed to measure the preoperative calcium levels, and the calcium levels were not corrected using the albumin levels. Furthermore, we failed to follow the patients and collect the calcium and PTH levels after one month for 25% and 40% of the cases and limited our analysis to the predictors of in-hospital hypocalcemia.

Conclusion

In this study we investigated several surgical, disease-related and patient-related and laboratory risk factors for developing transient hypocalcemia. We showed that the higher number of identified parathyroid gland is associated with lower incidence of hypocalcemia. Although more studies are needed to resolve this open debate, we suggest that surgeons attempt to identify all parathyroid glands if possible. We also showed that the change in PTH levels from baseline one and 24 hours after the surgery and not the absolute values of PTH was predictive of transient hypocalcemia. Based on the current evidence, we believe that the percent change in PTH levels should be more emphasized in predicting post-TT hypocalcemia.

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